PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

To:

SANTORO, Tiziana
Marietti e Gislon S.r.l.
Via Larga, 16
I-20122 Milan
ITALIE

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

Date of mailing (day/month/year) 13 March 2002 (13.03.02)	
Applicant's or agent's file reference 7587/2053 TS	**IMPORTANT NOTIFICATION**
International application No. PCT/IB00/01280	**International filing date** (day/month/year) 08 September 2000 (08.09.00)

1. The following indications appeared on record concerning:

[X] the applicant [ ] the inventor [ ] the agent [ ] the common representative

Name and Address	State of Nationality	State of Residence
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[X] the person [X] the name [ ] the address [ ] the nationality [ ] the residence

Name and Address	State of Nationality	State of Residence
PENTAPHARM LTD. Engelgasse 109 CH-4052 Basel Switzerland	CH	CH
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

3. Further observations, if necessary:
The above-mentioned name is the applicant for all designated states except the U.S.A. The inventor becomes the applicant and inventor for the U.S.A. only.

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[ ] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[X] the elected Offices concerned
[ ] other:

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Kiwa MPAY
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark
Office, PCT
2011 South Clark Place Room
CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 01 May 2001 (01.05.01)	
International application No. PCT/IB00/01280	**Applicant's or agent's file reference** 7587/2053 TS
International filing date (day/month/year) 08 September 2000 (08.09.00)	**Priority date** (day/month/year) 09 September 1999 (09.09.99)
Applicant GHISALBERTI, Carlo	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

12 March 2001 (12.03.01)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer S. Mafla
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION** see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
7587/2053 TS		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/IB 00/01280	08/09/2000	09/09/1999
Applicant		
GHISALBERTI, Carlo		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 2 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [ ] the text is approved as submitted by the applicant.

   [X] the text has been established by this Authority to read as follows:

   USE OF CONJUGATED LINOLEIC ACID (CLA9 FOR THE TOPICAL TREATMENT OF CELLULITE

5. With regard to the **abstract,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. _____

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [X] None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No
PC[redacted] 00/01280

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K7/48

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
WPI Data, PAJ, EPO-Internal, CHEM ABS Data, MEDLINE, EMBASE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	WO 00 01351 A (TRANSDERMAL TECHNOLOGIES) 13 January 2000 (2000-01-13) claims 1-11,17; examples 10,12	1-10
A,P A	EP 1 010 424 A (OTSUKA PHARMACEUTICAL CO) 21 June 2000 (2000-06-21) the whole document & WO 99 12538 A 18 March 1999 (1999-03-18)	1-10
A	WO 99 32105 A (BIO-TECHNICAL RESOURCES) 1 July 1999 (1999-07-01) the whole document	1-10

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 January 2001	22/01/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Fischer, J.P.

1

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/GB 00/01280

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0001351 A	13-01-2000	AU 4972599 A	24-01-2000
EP 1010424 A	21-06-2000	JP 11079987 A	23-03-1999
		WO 9912538 A	18-03-1999
WO 9932105 A	01-07-1999	AU 2091099 A	12-07-1999
		EP 1041979 A	11-10-2000
		US 6136985 A	24-10-2000

37

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
7587/2053 TS		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/IB 00/01280	08/09/2000	09/09/1999
Applicant		
GHISALBERTI, Carlo		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 2 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

[ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

[ ] contained in the international application in written form.

[ ] filed together with the international application in computer readable form.

[ ] furnished subsequently to this Authority in written form.

[ ] furnished subsequently to this Authority in computer readble form.

[ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

[ ] the text is approved as submitted by the applicant.

[X] the text has been established by this Authority to read as follows:

USE OF CONJUGATED LINOLEIC ACID (CLA9 FOR THE TOPICAL TREATMENT OF CELLULITE

5. With regard to the **abstract**,

[X] the text is approved as submitted by the applicant.

[ ] the text has been established, according to Rule 38.2(b), by this Authority as it app ars in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. _____

[ ] as suggested by the applicant.

[ ] because the applicant failed to suggest a figure.

[ ] because this figure better characterizes the invention.

[X] None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 00/01280

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K7/48

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
WPI Data, PAJ, EPO-Internal, CHEM ABS Data, MEDLINE, EMBASE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	WO 00 01351 A (TRANSDERMAL TECHNOLOGIES) 13 January 2000 (2000-01-13) claims 1-11,17; examples 10,12	1-10
A,P A	EP 1 010 424 A (OTSUKA PHARMACEUTICAL CO) 21 June 2000 (2000-06-21) the whole document & WO 99 12538 A 18 March 1999 (1999-03-18)	1-10
A	WO 99 32105 A (BIO-TECHNICAL RESOURCES) 1 July 1999 (1999-07-01) the whole document	1-10

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 January 2001	22/01/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Fischer, J.P.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Interna[redacted] Application No
PCT[redacted] 00/01280

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0001351 A	13-01-2000	AU 4972599 A	24-01-2000
EP 1010424 A	21-06-2000	JP 11079987 A	23-03-1999
		WO 9912538 A	18-03-1999
WO 9932105 A	01-07-1999	AU 2091099 A	12-07-1999
		EP 1041979 A	11-10-2000
		US 6136985 A	24-10-2000

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
7587/2053		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/IB00/01280	08/09/2000	09/09/1999
International Patent Classification (IPC) or national classification and IPC A61K7/48		
Applicant GHISALBERTI, Carlo		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 1 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☒ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
12/03/2001	12.12.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Vermeulen, S Telephone No. +49 89 2399 7520

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/IB00/01280

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-19	as originally filed	

Claims, No.:

1-10	with telefax of	28/11/2001

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   - ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   - ☐ the language of publication of the international application (under Rule 48.3(b)).
   - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   - ☐ contained in the international application in written form.
   - ☐ filed together with the international application in computer readable form.
   - ☐ furnished subsequently to this Authority in written form.
   - ☐ furnished subsequently to this Authority in computer readable form.
   - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   - ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   - ☐ the description, pages:
   - ☐ the claims, Nos.:
   - ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 10.

because:

☒ the said international application, or the said claims Nos. 10 relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-10
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-10
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-9

No: Claims no opinion: 10

2. Citations and explanations
see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

R It m III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claim 10 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. The present wording of said claim does not exclude methods of therapeutical treatment of the human or animal body. Consequently, no opinion is given with respect to the industrial applicability of the subject-matter of claim 10 (Article 34(4)(a)(i) PCT).

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1: WO 00 01351 A (TRANSDERMAL TECHNOLOGIES) 13 January 2000 (2000-01-13)

D2: WO 99 32105 A (BIO-TECHNICAL RESOURCES) 1 July 1999 (1999-07-01)

The following document was not cited in the international search report. Said document is cited by the applicant in the present application on page 2 (line 15) of the description:

D3: WO 9817269 A (KAPPA PHARMACEUTICALS LTD) 30 April 1998 (30.04.98)

The subject-matter of claims 1-10 meets the novelty and inventive step requirements of the PCT (Art. 33(2)-(3)). The use of CLA or a derivative thereof for the treatment and/or prophylaxis of fatty deposits and cellulite has not been disclosed nor suggested in the prior art. Also a topical composition comprising CLA or derivatives thereof in association with one or more common anti-cellulite agents is not disclosed in the prior art. Prior art document **D2 (page 2, lines 12-25 ; page 5, lines 31-35)** and **D3 (example A)** do indeed disclose compositions comprising CLA and derivatives thereof, however they do not contain any indication to associate said CLA to an anti-cellulite agent, nor do they suggest the use of CLA as an anti-cellulite agent. Accordingly the subject-matter of claims 1-10 is novel and inventive over documents D2-D3.

Re Item VI

Certain documents cited

Document **D1** , published after the effective date of application of the present application, contains subject-matter being relevant to claims 1-10 (Rule 70.10).

Application No Patent No	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date *(valid claim)* *(day/month/year)*
PCT/US99/15297	13/01/00	07/07/99	07/07/98

CLAIMS

1. Use of Conjugated Linoleic Acid or a derivative thereof (CLA) for the topical treatment and/or prophylaxis of fatty deposits and cellulite.

2. A cosmetic or dermatological topical composition, which comprises Conjugated Linoleic Acid or a derivative thereof (CLA) for the treatment and/or prophylaxis of fatty deposits and cellulite.

3. Cosmetic or dermatological topical composition according to claim 2, which comprises from 0.5 to 70% by weight of CLA.

4. Cosmetic or dermatological topical composition according to claims 2 or 3, wherein CLA derivatives comprise one or more cis and trans isomers of the 9,11- 10,12- and 11,13-octadecadienoic acids, its phospholipid and its mono-, di- and tri-glycerides, ethers, esters or salts thereof.

5. Cosmetic or dermatological topical composition according to claims 2 to 4, wherein CLA salts are metallic soaps of alkaline and earthy-alkaline ions and the nitrogen-containing salts.

6. Cosmetic or dermatological topical composition according to claims 2 to 5, in the form of a cream, gel, lotion, oil or spray, optionally comprising one or more further common anti-cellulite agents.

7. Cosmetic or dermatological topical composition according to claim 6, wherein the common anti-cellulite agent agent is a xanthine.

8. Cosmetic or dermatological topical composition according to claim 7, wherein the common anti-cellulite is selected among caffeine, theophylline, theobromine, aminophylline and mixture thereof.

9. Cosmetic or dermatological topical composition according to claims 2 to 8 which further comprises a vanadium compound.

10. Method of treatment and/or prophylaxis of fatty deposits and cellulite which comprises topically administering Conjugated Linoleic Acid or a derivative thereof (CLA) or a composition according to claims 2 to 9.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 00/01280

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K7/48

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
WPI Data, PAJ, EPO-Internal, CHEM ABS Data, MEDLINE, EMBASE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	WO 00 01351 A (TRANSDERMAL TECHNOLOGIES) 13 January 2000 (2000-01-13) claims 1-11,17; examples 10,12	1-10
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A	WO 99 32105 A (BIO-TECHNICAL RESOURCES) 1 July 1999 (1999-07-01) the whole document	1-10

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 January 2001	22/01/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Fischer, J.P.

1

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/GB 00/01280

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0001351 A	13-01-2000	AU 4972599 A	24-01-2000
EP 1010424 A	21-06-2000	JP 11079987 A	23-03-1999
		WO 9912538 A	18-03-1999
WO 9932105 A	01-07-1999	AU 2091099 A	12-07-1999
		EP 1041979 A	11-10-2000
		US 6136985 A	24-10-2000

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
15 March 2001 (15.03.2001)

PCT

(10) International Publication Number
WO 01/17498 A1

(51) International Patent Classification[7]: A61K 7/48

(21) International Application Number: PCT/IB00/01280

(22) International Filing Date:
8 September 2000 (08.09.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
MI99A001894 9 September 1999 (09.09.1999) IT

(71) Applicant and
(72) Inventor: GHISALBERTI, Carlo [BR/BR]; Rua Luis Dias, 85/61, Itaim-Bibi, CEP-04542-080 São Paulo, SP (BR).

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(54) Title: USE OF CONJUGATED LINOLEIC ACID (CLA) FOR THE TOPICAL TREATMENT OF CELLULITE

(57) Abstract: The present invention relates to the use of conjugated linoleic acid (CLA) for the topical treatment of fatty deposits and cellulite and to new topical compositions and to cosmetic and dermatological topical compositions for the treatment of fatty deposits and cellulite comprising CLA as well as kits comprising CLA for said treatment.

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USE OF CONJUGATED LINOLEIC ACID (CLA) FOR THE TOPICAL TREATMENT OF CELLULITE

FIELD OF THE INVENTION

The present invention relates to the use of conjugated linoleic acid (CLA) for the topical treatment of fatty deposits and cellulite and to new topical compositions.

More particularly, the invention relates to cosmetic and dermatological topical compositions for the cosmetic treatment of fatty deposits and cellulite comprising CLA as well as kits comprising CLA for said treatment.

BACKGROUND OF THE INVENTION

Conjugated linoleic acid (CLA) is a mixture of positional and configurational isomers of octadecadienoic acid, which are naturally occurring substances found in milk and diary products as well as in meats of ruminants.

The term CLA includes the family of positional and configurational isomers of C18:2 fatty acid, more precisely the cis and trans form of 9,11- 10,12- and 11,13-octadecadienoic acids.

Many studies reported that synthetic CLA is an effective agent in inhibiting mammary, colon, forestomach, and skin carcinogenesis in experimental models, due to its modulation of lymphocyte and macrophage activities. Recent clinical and in vivo data disclosed novel biological effects of CLA, e.g. the anti-atherogenic and anti-hyperinsulinemic activities.

After having attracted the attention of the international scientific

community for its therapeutic properties above, CLA is gaining further consumer acceptance as nutritional supplement as it has been shown that a CLA-enriched diet produces a significant improvement in overall health conditions.

CLA is also known as a slimming agent, whose oral consumption produces a marked decrease of body fat with increase in the lean body mass. The effects of CLA on body fat/lean ratio seem to be due to inhibition of both proliferation and differentiation of preadipocytes, as observed by Brodie A.E. et al. in J. Nutr. 129:602-6 (1999).

The use of CLA in topical composition and cosmetic method for treating skin conditions selected from the group consisting of wrinkling, sagging, photodamaged skin, sensitive skin, dry skin, flaky skin, red skin, irritated skin, itchy skin and age spots, is disclosed in WO0037040.

Topical compositions of zinc salts of CLA for the treatment of skin disorders, such as eczema, psoriasis and dermatitis and so on WO98/17269 discloses. However, the use of zinc salts of CLA is limited to pharmaceutical and dermatological purposes only. Moreover, the poor solubility of the zinc salts of CLA, either in lipophilic and hydrophilic media, significantly decreases the bioavailability of the active ingredient in said topical treatment.

DETAILED DESCRIPTION OF THE INVENTION

It is appreciated that in the present specification the term CLA is intended to include either CLA in the form of free fatty acid or its derivatives, such as its phospholipid, its mono-, di- and tri-glycerides, ethers, esters or salts thereof. All derivatives must be physiologically acceptable, i.e. non-toxic derivatives of CLA. Preferred salts of CLA include the metallic soaps of CLA

with alkaline and/or earth-alkaline ions, such as sodium, potassium, or magnesium ions, and the nitrogen-containing salts, such as ammonia, mono-, di- or tri-ethanolamine.

We have first envisaged the possibility to use CLA in the treatment of cellulite, the skin dimpling of the thighs and buttocks caused by dermohypodermosis and oedemato-sclerous panniculopathy, in which the fibroblastic reaction predominates over capillaro-veinular changes.

As observed by Rosenbaum M; Prieto V; Hellmer J; Boschmann M; Krueger J; Leibel RL; Ship AG (Plast Reconstr Surg, 101(7):1934-9 1998), in vitro pathologic examination of wedge biopsies and in vivo sonographic examination of the thigh both showed a diffuse pattern of extrusion of underlying adipose tissue into the reticular dermis.

Adipocytes of exaggerated size interpenetrate into micronodules and later into macronodules marked off by more or less structured conjunctive fibrilla, as quoted by Merlen JF; Curri SB; Sarteel AM (Phlebologie, 32(3):279-82, 1979).

Due the uncertainty of cellulite aetiology, said unaesthetic condition has been so far treated with a variety of active ingredients, each acting by different mechanisms.

We have now found out that the topical administration of CLA accelerates and provokes the reduction of fatty deposits.

We have consequently found out that CLA is effective in the topical treatment of the impaired aesthetic conditions caused by subcutaneous fat deposition, particularly on pannicular adiposis, said topical treatment leading to a significant improvement of the cellulite conditions.

Therefore, one of the objects of the present invention is the use of CLA for the topical treatment and/or prevention of fatty deposits and cellulite.

CLA is particularly suitable for the topical anticellulite treatment; it is a natural product which showed no observed adverse effects or toxicity in humans after topical treatment. After several applications on people of both sexes having derma either in normal or in pathological status, e.g. erythema and itching derma, no phenomena showing intolerance to the product occurred.

The physical and chemical properties of CLA are particularly appropriate for a topical skin treatment, as it displays good lipid solubility and is easily absorbed onto the horny layer.

According to another of its aspects, the present invention concerns a cosmetic and dermatological topical composition, useful for treating and/or preventing cellulite and fatty deposits.

According to a further aspect, the invention concerns a method for the treatment of cellulite which comprises topically administering to a subject an effective amount of CLA, either alone or in the form of a topical composition.

In order to exploit the cosmetic treatment of the invention CLA is preferably administered in the form of a topical composition, said composition having a content of CLA of from 0.5 to 70% by weight, preferably from 1 to 30% by weight, more preferably from 2 to 5% by weight, optionally in admixture with suitable customary auxiliary agents.

In a preferred embodiment of the present invention, CLA is combined with one or more well-known anti-cellulite agent.

Particularly preferred common common anti-cellulite agents are substances showing beta-stimulation (adrenergic beta-agonists) to further enhance lipolysis into the dermal adipocytes. Examples of such substances are xanthines such as caffeine, theophylline, theobromine and aminophylline, which are characterized by a high skin availability and an high efficacy. Xanthines are preferably employed in an proportion of at least 0.05%, generally in an proportion of from 0.05% to 20%, preferably from 0.10% to 10%, optimally from 0.5% to 3.0% by weight of the composition in order to maximize efficacy at optimum cost.

Other preferred common anti-cellulite agents are substances acting as collagen synthesis stimulators, such as ascorbates and triterpenoids of Centella asiatica, e.g. asiatic acid, madecassic acid, asiaticoside, madecaside, inositol phosphate, and phytic acid.

Other preferred common anti-cellulite agent are substances which improve the poor vascularity condition associated to the cellulitic areas by a vasokinetic activity, such as minoxidil, nicotinates, escin, ivy, and methyl salicylate.

Other preferred common anti-cellulite agent are natural substance exerting adenylate cyclase agonist and/or anti-phosphodiesterase activities, which accelerate the reduction of fatty deposits located in the cellulite affected area. The former group may include extracts from Ipomea spp., from Salvia spp. and from Rosmarinus officinalis, the latter group the yohimbine-type alkaloids and those plant extracts (e.g. ginkgo biloba) which contain dimeric flanones such as amentoflavone, bilobetine, sciadopitisine, ginkgonetine, or extracts from some Malvaceae (e.g. Malva, Althea,

Hibiscus, Hoheria, Sidalcea, Abutilon and Gossypium).

For the treatment of cellulite and fatty deposits, topical CLA may also be used in combination with vanadium compounds.

Vanadium compounds are known to act as insulin-mimetic substances, thus as being capable to enhance glycolisis and metabolic turn-over in cells, including adipocytes.

Therefore, according to a particular embodiment, the present invention relates to a cosmetic composition comprising CLA and at least a vanadium compound.

Vanadium (IV) or (V) compounds are suitably present at concentration in the range of 10^{-10} to 10^{-3} moles/kg, preferably 10^{-7} to 10^{-5} moles/kg in the cosmetic compositions of the present invention.

Illustrative examples of suitable vanadium (V) compounds useful in the practice of the present invention include sodium metavanadate ($NaVO_3$), orthovanadate (Na_3VO_4) and pyrovanadate ($Na_4V_2O_7$), corresponding salts with potassium (KVO_4), ammonium (NH_4VO_3), calcium ($Ca_3(VO_4)_2$), iron ($Fe(VO_3)_3$), and corresponding salts of vanadates with magnesium, zinc, aluminum, and the like; the vanadium (V) oxides such as the pentoxide (V_2O_5), oxytrichloride ($VOCl_3$), oxytribromide ($VOBr_3$) and the like, as well as polymers such as a dimer ($H_2V_2O_7$), a trimer (V_3O_9), a decamer ($HV_{10}O_{28}$), and the like.

Illustrative examples of suitable vanadium (IV) compounds useful in the practice of the present invention include vanadyl sulfate ($VOSO_4$), and corresponding compounds with acetate, etc; vanadium (IV) oxyhalides such as the oxychloride ($VOCl_2$), oxydibromide ($VOBr_2$), and oxydifluoride (VOF_2);

vanadium (IV) halides such as the tetrachloride (VCl_4), tetrabromide (VBr_4) and tetrafluoride (VF_4) and the like; vanadium dioxide (VO_2) and vanadium tetraoxide (V_2O_4).

Furthermore, the vanadium (IV) or (V) compounds may be present in form of chelates, clathrates or other complexes, including those with amino acids, proteins, peptidic growth factors, nucleic acids, phosphates, phospholipids, fatty acids, prostaglandins, AHAs, retinoids, tris-edatate, glycols, catechols, glutathione, and the like.

The vanadium (IV) or (V) compounds may also be present as salts of organic acids and vanadium contained in tunicates (sea squirts), some mushroom species and plants, and other organic sources. Specific examples of vanadium organometallic compounds include vanadyl salts of organic acids such as: vanadyl linoleate, oleate, palmitate, phenolate, resinate and stearate.

All the compositions according to the invention may also comprise any cosmetically acceptable ingredients. The expression "cosmetically acceptable ingredients" designate in the present specification products which are suitable for their use in cosmetic treatments, for example those included in the INCI list drawn by the European Cosmetic Toiletry and Perfumery Association (COLIPA) and issued in 96/335/EC "Annex to Commission Decision of 8 May 1996".

A variety of active ingredients may further be added to the compositions according to the present invention. Although not limited to this category, general examples include anti-inflammatory agents and skin whitening agents, antioxidants and anti-wrinkling agents.

Suitable anti-inflammatory compounds include, but are not limited to, rosmarinic acid, glycyrrizinate derivatives, alpha bisabolol, azulene and derivatives thereof, asiaticoside, sericoside, ruscogenin, escin, escolin, quercetin, rutin, betulinic acid and derivatives thereof, catechin and derivatives thereof.

Suitable skin whitening compounds include, but are not limited to, ferulic acid, hydroquinone, arbutine, and kojic acid.

Suitable antioxidants and anti-wrinkling compounds include, but are not limited to, retinol and derivatives, tocopherol and derivatives, salicylates and their derivatives.

Another important agent which can be added in the cosmetic composition according to the invention is an alpha-hydroxy acid. Preferred alpha-hydroxy acids are monocarboxylic acids, improving skin penetration and efficacy of CLA and further common anticellulite agents, such as lactic acid, glycolic acid, mandelic acid and mixtures thereof. Preferably, the proportion of the alpha-hydroxy acid component in the cosmetic composition of the invention is from 1.5% to 15%, more preferably from 3.0% to 12.0% by weight of the composition.

Another important optional ingredient is chosen among essential fatty acids (EFAs), exerting an important role in skin defence against oxidative stress, by entering in the lipid biosynthesis of epidermis and providing lipids for the barrier formation of the epidermis. Preferred essential fatty acids are selected from the group consisting of linoleic acid, gamma-linolenic acid, homo-gamma-linolenic acid, columbinic acid, eicosa-(n-6,9, 13)-trienoic acid, arachidonic acid, gamma-linolenic acid, timnodonic acid, hexaenoic

acid and mixtures thereof.

The cosmetic compositions of the invention can further comprise substances acting as dilutant, dispersant or carrier for CLA which are added to the compositions according to well known techniques in any suitable proportion well known to the skilled in the art, for example ranging from about 30% to about 99.9%, preferably from about 50 to 99.5% by weight of the total composition.

An oil or oily material may be present with water together with an emulsifier (alias "surfactant") to provide either w/o or o/w emulsions, largely depending on the average hydrophilic-lipophilic balance (HLB) of the emulsifier. Surfactants can be incorporated in any suitable proportion well known to the skilled in the art, for example from about 0.5% to about 30%, preferably from about 1% to about 15% by weight.

Cationic, nonionic, anionic, or amphoteric surfactants, and combinations thereof may also be employed. Nonionic surfactants may include alkoxylated compounds based upon fatty alcohols, fatty acids and sorbitan, copolymers of polyoxypropylene-polyoxyethylene, and alkyl polyglycosides. Anionic-type surfactants may include fatty acid soaps, sodium lauryl sulphate, sodium lauryl ether sulphate, alkyl benzene sulphonate, mono and/or dialkyl phosphates and the like. Amphoteric surfactants include dialkylamine oxides, various types of betaines and natural phospholipids.

In a water-based cosmetic composition, a thickener agent may also be present in any suitable proportion well known to the skilled in the art, for example from 0.1 to 10% by weight, preferably from about 0.5% to 5% by

weight. Exemplary thickener agent are cross-linked polyacrylate materials (Carbopol®), and gums such as xanthan, carrageenan, gelatin, karaya, pectin and locust beans gum. Said water-based cosmetic composition can be protected with preservatives against the growth of microorganisms. Suitable preservatives include alkyl esters of p-hydroxybenzoic acid, hydantoin derivatives, propionate salts, methyl paraben, propyl paraben, imidazolidinyl urea, sodium dehydroxyacetate benzyl alcohol, and a variety of quaternary ammonium compounds. Preservatives are added any suitable proportion well known to the skilled in the art, for example in proportion ranging from about 0.2% to 1% by weight.

In a fluid non-aqueous cosmetic composition, silicone polymers may also be present, in any suitable proportion well known to the skilled in the art, for example in amounts of ranging from 5 to 95% by weight.

Further ingredients that may be included in the cosmetic composition of the present invention are emollients. Under certain circumstances emollients may have dual functionality, acting both as carrier, to facilitate the dispersion of the CLA as active ingredient and skin softners. Emollients may be incorporated in the cosmetic composition of the invention in any suitable proportion well known to the skilled in the art, for example ranging from about 0.5% to about 50%. Suitable emollients may be classified under such general chemical categories as esters, fatty acids and alcohols, polyols and hydrocarbons. Appropriate fatty di-esters include dibutyl adipate, diethyl sebacate, diisopropyl dimerate, propylene glycol myristyl ether acetate, diisopropyl adipate, and dioctyl succinate. Appropriate branched chain fatty esters include 2-ethyl-hexyl myristate, isopropyl stearate and

isostearyl palmitate. Appropriate tribasic acid esters include triisopropyl trilinoleate, trilauryl citrate, tributirrine, and saturated or unsaturated vegetable oils. Appropriate straight chain fatty esters include lauryl palmitate, myristyl lactate, oleyl eurcate, stearyl oleate coco-caprylate/caprate, and cetyl octanoate. Appropriate fatty alcohols and acids are C_{10}-C_{20} compounds such as cetyl, myristyl, palmitic and stearyl alcohols and acids. Appropriate polyols are linear and branched chain alkyl polyhydroxyl compounds, such as propylene and butylene glycol, sorbitol glycerin, as well as polymeric polyols such as polypropylene glycol and polyethylene glycol. Appropriate hydrocarbons are linear C_{12}-C_{30} hydrocarbon chains such as mineral oil, petroleum jelly, squalene and isoparaffins.

Sunscreens may also be incorporated in the cosmetic composition of the invention. Illustrative compounds are the derivatives of PABA, cinnamate and benzophenone such as octyl methoxy-cinnamate, 2-hydroxy-4-methoxy-benzophenone. The proportion of sunscreens employed depends upon the degree of protection desired from the UV radiation.

Other minor components may also be added to the cosmetic composition of the invention, including colouring agents, opacifiers and perfumes each being optionally present in appropriate proportions for example from 0.001% up to 20% by weight of the composition.

The topical skin treatment composition of the invention can be formulated as a lotion, a fluid cream, a cream or a gel. The composition can be packaged in a suitable container according to its viscosity and to the intended use by the user. For example, a lotion or fluid cream can be

packaged in a bottle, in a roll-ball applicator, in a capsule, in a propellant-driven aerosol device or a container fitted with a pump suitable for finger operation. When the composition is a cream, it can simply be stored in a non-deformable bottle or in a squeeze container, such as a tube or a jidded jar.

According to another of its aspects the present invention relates to a kit for the topical administration of CLA.

Said kit comprises (a) unit dosage form compositions comprising CLA, optionally in admixture with suitable customary excipients and antioxidants, preferably in the form of an oily liquid and (b) unit dosage form comprising at least one hydrophilic anticellulite agent, optionally in admixture with suitable customary excipients and alpha-hydroxy acid, in aqueous or hydroalcoholic solution.

The kit packaging box further comprises an leaflet giving the instruction to apply first the aqueous solution (b) for the effective absorption of the hydrophilic ingredients, and secondly to apply the oily liquid (a).

One of the advantages of the kit is that the penetration of hydrophilic anticellulite agents is made easier in absence of the oily phase, which is subsequently applied to the skin.

The following examples show in detail how the present invention can be practiced but should not be intended as limiting it.

Preparative Example 1 - Synthesis of CLA by alcaline isomerization of grape seed oil in glycerol (The following synthesis makes the object of a co-pending application).

1 kg glycerol, 235 g potassium hydroxide (KOH) and 1000 g of grape seed oil were added into a 4-neck round bottom flask (5000 ml) equipped with a mechanical stirrer, a thermometer, a reflux condenser, and a nitrogen inlet, the nitrogen being introduced in first run through two oxygen traps.

Nitrogen was bubbled into the reaction mixture for 20 min and the temperature was then raised to 90-100 °C, and kept under mechanical stirring for about 20 minutes to convert the trigliceride in the corresponding potassium salts. The double phase system disappears to form a glyceric soap suspension, then heated at 230 °C under inert atmosphere and stirred for 4 hours.

The reaction mixture was cooled to about 100 °C, and the stirring stopped as the reaction mixture tend to reach very high viscosity during cooling. 2 l of water was then slowly added, and the mixture kept at 95°C for 2 hour. This operation becomes necessary because of the neglegible presence of water and high content of glycerol causing fatty acids to be present as mono- and diglyceride from 5% to 10% by weight of the total lipid content. As partial glyceride esters tend to form W/O emulsion, the water addition and re-heating provides full saponification of the residual esterified fatty acid.

The mixture was transferred into a becker, then cooled to room temperature and 50% w/v sulfuric acid was added to the mixture which was stirred for 1 hour until the pH stabilized at about 3.

The acidulated oil phase formed a lower hydroglyceric layer and an upper fatty acid oil layer containing CLA, which was separated by decantating. Noteworthy, in industrial operation the separation could be

carried out by centrifugation.

The CLA was washed with water and finally it was made anhydrous with sodium sulphate and filtered, then it is stored in a dark bottle at 4 °C until time of use. Total yield about 770 g af an amber oil, whose GC-analysis is shown in Table 1.

TABLE 1

Fatty Acid	Grape Seed (Starting material)	CLA from Grape Seed (Final Product)
C14:0	0.11	0.13
C16:0	6.53	6.56
C18:0	3.02	3.23
C20:0	0.19	0.20
total saturated	9.85	10.12
C16:1	0.42	0.48
C18:1	16.42	17.15
C18:1(t)	0.08	0.23
C20:1	0.59	0.60
total monounsaturated	17.51	18.46
C18:2	72.11	1.76
C18:2-conjugated (CLA)	0.21	69.48
C18:3	0.31	0.18
C20:3	0.01	0.00
total polyunsaturated	72.64	71.42

The composition of CLA appears to be a complex mixture, i.e. 9c,11t- and 8c,10t- octadecadienoic acids at 30,90 %, 11c,13t- 10t,12c- octadecadienoic acids at 32,05 %, 11t,13c- 8c,10c- 9c,11c- octadecadienoic acid at 1,55 %, 10c,12c- 11c,13c- 11t,13t , 9t,11t- 10t,12t- 8t,10t- octadecadienoic acids making the remaining part.

Comparative Example 1 and Applicative Examples 1, 2 – Body creams

Three different O/W emulsions were prepared under stirring by turbomixing the oily phase and the water phase, each separatedly preheated at 75° C; the compositions are shown herewithafter:

Ingredient	Emulsion of Comparative Example 1	Emulsion of Applicative Example 1	Emulsion of Applicative Example 2
Oily phase			
CLA from the Preparative Example 1	-	2.7 g	2.7 g
soybean fatty acids	2.7 g	-	-
poliglyceryl-2-sesquistearate	1.0 g	1.0 g	1.0 g
bees wax	0.3 g	0.3 g	0.3 g
magnesium stearate	0.5 g	0.5 g	0.5 g
aluminum stearate	0.5 g	0.5 g	0.5 g
hydrogenated castor oil 7-PEO	2.0 g	2.0 g	2.0 g
liquid paraffine	10.0 g	10.0 g	10.0 g
methyl p-hydroxybenzoate	0.1 g	0.1 g	0.1 g
18-beta-glycirretic acid	1.0 g	1.0 g	1.0 g
alpha-tocopheryl acetate	0.5 g	0.5 g	0.5 g
BHT	0.3 g	0.3 g	0.3 g

Aqueous phase			
glycolic acid	3.0 g	3.0 g	3.0 g
matè extract (caffeine 7%)	-	-	2.0 g
decaffeinated matè extract	2.0 g	2.0 g	-
ascobic acid (vitamin C)	0.01 g	0.01 g	0.01 g
deionized water q.b.	to 100 g	to 100 g	to 100 g

As it can be noted, the topical formulations contain no CLA, CLA alone, and CLA with caffeine, respectively.

Applicative Exemple 3 – Clinical trial of anticellulite activity by topical application of CLA and CLA with a xantine

9 female subjects were selected based on their cellulite intensity in the thigh area having a bi-lateral symmetry. Subjects with grades 1 and 2 cellulite were chosen, as a 5-point grading scale was used to rate the cellulite severity of each subject. The scale ranged from 0 to 4, being 0 = No cellulite; 1 = Small bumps or depressions; 2 = Striations and bumps; 3 = Pronounced lumpiness of the skin and striations; 4 = All of the above plus hard sub-surface nodules.

The subjects were divided in 3 groups of 3 individuals each, and instructed to apply in the right thigh the compositions of Comparative Example 3, the one of Applicative Example 4, and the one of Applicative Example 5, respectively.

The subject were taught to carried out the application two times a day, at morning and at night, during 2 months. Afterwards the cellulite condition were evaluated according Smith WP (Cosmetics & Toiletries, 61-70, June 1995), by comparison of the right thigh versus left thigh. Results are

illustrated in Table 2.

TABLE 2

Change of the cellulite condition after 2 month application

Condition	Cream of Comparative Example 3	Cream of Applicative Example 4	Cream of Applicative Example 5
Thigh diameter	-1%	-5%	-8%
Fatty layer thickness	-3%	-18%	-24%
Subjective improvement	+10%	+33%	+50%
Clinical grading	+2%	+30%	+30%
Skin firmness	+5%	+10%	+15%
Irritation reactions	2	0	3
Skin hydration	+25%	+13%	+24%
Surface smoothness	+14%	+21%	+37%

The results above show that the composition containing CLA effectively ameliorate the cellulite condition, with a further improvement by the combination with caffeine.

Applicative Example 4 – Kit for the cellulite treatment

An oily mixture (a) and a hydroalcoholic solution (b) were separately prepared by blending the following ingredients:

a) Ingredient of the oily mix

CLA from the Preparative Example 1	1.50 g
soya sterols	0.25 g
butylene glycol	1.50 g

vitamin E acetate	0.20 g
vitamin A palmitate	0.20 g
alpha bisabolol	0.10 g
asiaticoside	0.15 g
ethyl alcohol 94°	5.00 g
almond oil	q.b. to 20.00 ml

a) Ingredient of the aqueous mix

tributyl citrate	0.15 g
caffeine	0.15 g
ginkgo biloba extract	0.50 g
green tea extract	0.10 g
theophylline	0.20 g
glycolic acid	3.00 g
escin	0.05 g
18-beta-glycirretic acid	0.03 g
disodium EDTA	0.02 g
ethyl alcohol 94°	2.00 g
demineralized water	q.b. to 20 ml (*)

(*) Due to the low pH value, preservatives are not needed.

The two compositions were separately bottled in 25 ml jars and combined in the same kit package, along with the instruction to firstly apply (b) and, after 10 minutes to apply (a).

It should be understood that the specific forms of the invention herein illustrated and described are intended to be representative only. Changes, including but not limited to those suggested in this specification, may be

made in the illustrated embodiments without departing from the clear teachings of the disclosure. Accordingly, reference should be made to the following appended claims in determining the full scope of the invention.

5

CLAIMS

1. Use of Conjugated Linoleic Acid or a derivative thereof (CLA) for the topical treatment and/or prophylaxis of fatty deposits and cellulite.

2. A cosmetic or dermatological topical composition, which comprises Conjugated Linoleic Acid or a derivative thereof (CLA) for the treatment and/or prophylaxis of fatty deposits and cellulite.

3. Cosmetic or dermatological topical composition according to claim 2, which comprises from 0.5 to 70% by weight of CLA.

4. Cosmetic or dermatological topical composition according to claims 2 or 3, wherein CLA derivatives comprise one or more cis and trans isomers of the 9,11- 10,12- and 11,13-octadecadienoic acids, its phospholipid and its mono-, di- and tri-glycerides, ethers, esters or salts thereof.

5. Cosmetic or dermatological topical composition according to claims 2 to 4, wherein CLA salts are metallic soaps of alkaline and earthy-alkaline ions and the nitrogen-containing salts.

6. Cosmetic or dermatological topical composition according to claims 2 to 5, in the form of a cream, gel, lotion, oil or spray, optionally comprising one or more further common anti-cellulite agents.

7. Cosmetic or dermatological topical composition according to claim 6, wherein the common anti-cellulite agent agent is a xanthine.

8. Cosmetic or dermatological topical composition according to claim 7, wherein the common anti-cellulite is selected among caffeine, theophylline, theobromine, aminophylline and mixture thereof.

9. Cosmetic or dermatological topical composition according to claims 2 to 8 which further comprises a vanadium compound.

10. Method of treatment and/or prophylaxis of fatty deposits and cellulite which comprises topically administering Conjugated Linoleic Acid or a derivative thereof (CLA) or a composition according to claims 2 to 9.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
7587/2053		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/IB00/01280	08/09/2000	09/09/1999
International Patent Classification (IPC) or national classification and IPC A61K7/48		
Applicant GHISALBERTI, Carlo		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 1 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability: citations and explanations suporting such statement
   - VI ☒ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
12/03/2001	12.12.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Vermeulen, S Telephone No. +49 89 2399 7520

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/IB00/01280

I. Basis of the report

1. With regard to the elements of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-19 as originally filed

Claims, No.:

1-10 with telefax of 28/11/2001

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 10.

because:

☒ the said international application, or the said claims Nos. 10 relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-10
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-10
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-9

No: Claims no opinion: 10

2. Citations and explanations
see separate sheet

VI. **Certain documents cited**

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claim 10 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. The present wording of said claim does not exclude methods of therapeutical treatment of the human or animal body. Consequently, no opinion is given with respect to the industrial applicability of the subject-matter of claim 10 (Article 34(4)(a)(i) PCT).

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1: WO 00 01351 A (TRANSDERMAL TECHNOLOGIES) 13 January 2000 (2000-01-13)

D2: WO 99 32105 A (BIO-TECHNICAL RESOURCES) 1 July 1999 (1999-07-01)

The following document was not cited in the international search report. Said document is cited by the applicant in the present application on page 2 (line 15) of the description:

D3: WO 9817269 A (KAPPA PHARMACEUTICALS LTD) 30 April 1998 (30.04.98)

The subject-matter of claims 1-10 meets the novelty and inventive step requirements of the PCT (Art. 33(2)-(3)). The use of CLA or a derivative thereof for the treatment and/or prophylaxis of fatty deposits and cellulite has not been disclosed nor suggested in the prior art. Also a topical composition comprising CLA or derivatives thereof in association with one or more common anti-cellulite agents is not disclosed in the prior art. Prior art document **D2 (page 2, lines 12-25 ; page 5, lines 31-35)** and **D3 (example A)** do indeed disclose compositions comprising CLA and derivatives thereof, however they do not contain any indication to associate said CLA to an anti-cellulite agent, nor do they suggest the use of CLA as an anti-cellulite agent. Accordingly the subject-matter of claims 1-10 is novel and inventive over documents D2-D3.

Re Item VI

Certain documents cited

Document **D1** , published after the effective date of application of the present application, contains subject-matter being relevant to claims 1-10 (Rule 70.10).

Application No Patent No	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date *(valid claim)* *(day/month/year)*
PCT/US99/15297	13/01/00	07/07/99	07/07/98

CLAIMS

1. Use of Conjugated Linoleic Acid or a derivative thereof (CLA) for the topical treatment and/or prophylaxis of fatty deposits and cellulite.
2. Use of a topical composition which comprises Conjugated Linoleic Acid or a derivative thereof (CLA) for the treatment and/or prophylaxis of fatty deposits and cellulite.
3. Use according to claim 2, wherein the topical composition comprises from 0.5 to 70% by weight of CLA.
4. Use according to claims 2 or 3, wherein CLA derivatives comprise one or more cis and trans isomers of the 9,11- 10,12- and 11,13-octadecadienoic acids, its phospholipid and its mono-, di- and tri-glycerides, ethers, esters or salts thereof.
5. Use according to claim 4, wherein CLA salts are metallic soaps of alkaline and earthy-alkaline ions and the nitrogen-containing salts.
6. A cosmetic or dermatological topical composition which comprises Conjugated Linoleic Acid or a derivative thereof (CLA) in the form of a cream, gel, lotion, oil or spray, further comprising one or more further common anti-cellulite agents.
7. Cosmetic or dermatological topical composition according to claim 6, wherein said common anti-cellulite agent is a xanthine.
8. Cosmetic or dermatological topical composition according to claim 7, wherein said common anti-cellulite agent is selected among caffeine, theophylline, theobromine, aminophylline and mixture thereof.
9. A cosmetic or dermatological topical composition, which comprises Conjugated Linoleic Acid or a derivative thereof (CLA) for the treatment and/or prophylaxis of fatty deposits and cellulite, which further comprises a vanadium compound.
10. Method of treatment and/or prophylaxis of fatty deposits and cellulite which comprises topically administering Conjugated Linoleic Acid or a derivative thereof (CLA) or a composition according to claims 6 to 9.